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Molecular Mechanics Study of the Inclusion Complexes of Some 1,2,4-Oxadiazole Derivatives of 3,3′-Bis (1,2,4-Oxadiazol-5(4H)-one) with β-Cyclodextrin

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Key words: β-cyclodextrin, binding energy, host–guest interactions, inclusion complexes, molecular mechanics, oxadiazole derivatives

Abstract

Molecular mechanics calculations were employed to study the inclusion of some 1,2,4-oxadiazol derivatives in β-cyclodextrin in vacuum and in the presence of water as a solvent using MM + force field. The driving forces for complexation in both environments are dominated by nonbonded van der Waals host–guest interactions with little electrostatic contribution. Among 1,2,4-oxadiazole derivatives investigated in this work, 3,3́-bis(1,2,4-oxadiazol-5(4H)-one) (H_2OD) forms the least stable 1:1 complex and the stability increases as the chain length increases.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides with central hydrophobic cavities and hydrophilic exterior edges. Cyclodextrins are composed of 5 to 12 α-(1–4)-linked D (+) glucopyranose units linked in macrocyclic ring. The most widely used (CD's) are α-, β-, and γ-(CDs). The ability of β-CD to form inclusion complexes with different products is well known [1–9]. In particular, β-cylodextrin (β-CD) has an internal cavity shaped like a truncated cone of about 8 Å deep and 6.0–6.4 Å in diameter. This cavity possesses a relatively low polarity that can accommodate guest organic molecules inside. Formation of inclusion complexes of organic molecules with cyclodextrins is important for their pharmaceutical and technological applications [10]. Recently, there has been considerable interest in the computer modeling of cyclodextrins [11–21]. Their shapes, energies, and most probable geometries are typically computed. Molecular mechanics calculations are useful for a better understanding of such inclusion processes of cyclodextrins. The calculation can strengthen and supplement the conclusions from experiment, and vice versa [22]. In this paper we have been using molecular mechanics (MM) to study the inclusion phenomena of some new 1,2,4-oxadiazole derivatives, R_2OD [23] with β-CD in vacuum and in water.

Oxadiazole derivatives (R_2OD) investigated in this work are indicated below.

Computational methods

Molecular mechanics (MM) [17, 23–27] computational of guest/host interactions in vacuum and in water as a solvent were carried out using the hyperchem® molecular modeling software (release 7.15, 2003, Hypercube, Inc.) and MM + force field. A relative permittivity of 1.5 was used for electrostatic interactions. Minimization was performed using the conjugate gradient algorithm (0.1 and 3.0 kcal/mol-Å gradients for the calculations performed in vacuum and in water, respectively). Aqueous solvation was simulated through a cubic water box with periodic boundary conditions; the dimension of the box was in each case limited to the minimum dimension where interaction potentials fall to zero. The starting geometry of β-cyclodextrin was taken from the published X-ray diffraction data [28]. This structure was in turn minimized with the MM + force field. The geometry obtained at this stage did not show radial symmetry due to free rotations of the glucosyl rings about $C_1(n)$–$O_4(n-1)$, $O_4(n-1)$ and $O_4(n-1)$–$C_4(n-1)$ bonds.

A conformational analysis for R_2OD has been performed using MM + force field as depicted in Figure 1. The resulting lowest-energy conformation was further optimized at the HF *ab initio* level with the 3–21G* basis set leading to the conformational minima with the torsional angle N_4–C_3–C_3'–N_4' is in the trans state (I).

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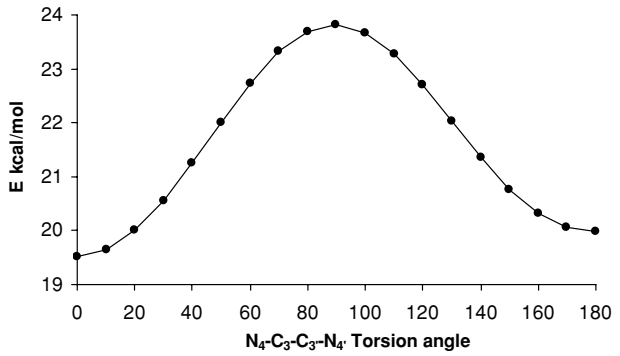

Figure 1. Conformational analysis of H_2OD arising from the rotation around the C_3–C_3' bonds.

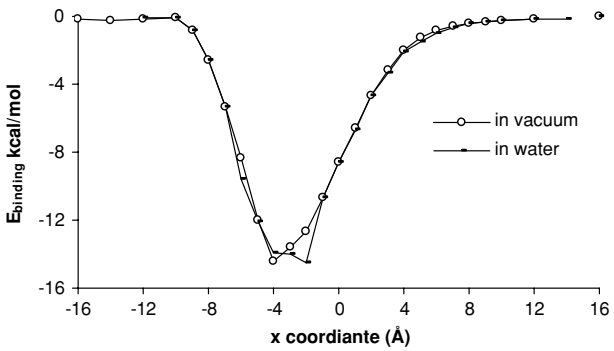

Figure 3. $E_{binding}$ for H_2OD:β-CD complex vs x coordinate (Å) in vacuum and water.

Results and discussion

The tertiary inertial axis of β-cyclodextrin was set at the x-axis, and the secondary inertial axis was set at the y-axis. The center of mass of the O_4 glucoside atoms polygon was located at the origin of the Cartesian coordinate.

Already individually optimized structures of the guest and cyclodextrin molecules (in vacuum) were allowed to approach each other along an axis (x axis) passing through the center of the cyclodextrin cavity. Starting at -16 Å, the energy of the guest was minimized all the way through $+16$ Å from the origin of the Cartesian coordinate, which was designated by the centre of ether glucosidic oxygens of cyclodextrin and an atom close the centre of mass of the guest molecule at 1 Å intervals (Figure 2). The structure generated at each step was then optimized, allowing them to change from the initial conformations, keeping the movement of the reference atoms and cyclodextrin structure totally restricted. At the energy minimum thus obtained, the 1:1 guest/β-CD complex was optimized free of any restrictions using an 0.01 kcal/mol-gradient to obtain optimal solute–ligand complex (SL complex) geometry.

The nonbonded interaction energy between the guest and cyclodextrin, or binding energy, $E_{binding}$, was estimated according to the relation

$$E_{binding} = E_{guest:\beta\text{-CD}} - (E_{isolatedguest} + E_{isolated}\beta\text{-CD})$$

where the terms on the right-hand side represent the potential energy of the guest: β-CD system minus the sum of potential energies of most stable conformation of isolated guest (trans state) and cyclodextrin. $E_{binding}$ in the presence of water was obtained by removing the water molecules from the box before applying the last relation [21].

As a typical example, Figure 3 shows the variation of the binding energy of H_2OD/β-CD system against the x-coordinate of the reference atom in H_2OD shown in the sketch below.

Figure 3 shows that the most stable configurations were observed at 4 and -2 Å distances for H_2OD in vacuum and water with a binding energies of 14.41 and -14.51 kcal/mol, respectively (Tables 1 and 2). After removing all restrictions on the system, the binding energies corresponding to optimal SL complexes configuration were $\sim$20.57 and $\sim$17.23 kcal/mol in vacuum and water, respectively (Table 3).

A breakdown of the binding energy to overall van der Waals and electrostatic contributions is plotted in Figure 4 for H_2OD in vacuum. In this case, complex stability is dominated by van der Waals interactions with little electrostatic contribution. The various contributions to complex stability at the minimum energy and infinite separation stemming from electrostatic, van der Waals and stretching plus torsion interactions are listed in Tables 1 and 2 for both vacuum and water, respectively.

Aside from minor differences in some conformational adjustment to β-CD, the optimal complex

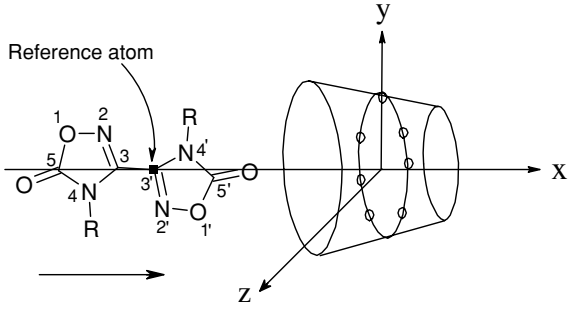

Figure 2. Scheme representation for the path of R_2OD complexation with β-CD.

Table 1. $E_{binding}$ at the minimum energy and at the largest separation for H_2OD in vacuum*

Energy, kcal/mol	H_2OD_{min}	H_2OD_{∞}
$E_{binding}$	−14.41	−0.145
Electrostatic part	−3.05	−0.086
Van der Waals part	−11.36	−0.059
E_{tot} for H_2OD/β-CD	127.62	141.71
Electrostatic part	−30.78	−27.83
Van der Waals part	23.41	34.70
Stretching + bending + torsion	134.99	134.84
E_{tot} for β-CD	122.33	122.19
Electrostatic part	−13.92	−13.88
Van der Waals part	35.31	35.11
Stretching + bending + torsion	100.94	100.96
E_{tot} forH_2OD	19.70	19.36
Electrostatic part	−14.04	−14.04
Van der Waals part	−0.48	−0.47
Stretching + bending + torsion	34.22	33.87

* The reference atom and β-CD structure are totally restricted.

configurations obtained in vacuum and in water look quite similar. The most favorable interaction between H_2OD, Me_2OD and Et_2OD and β-CD in both vacuum and water involves with carbonyl groups interacting with the hydroxyl groups located at the both rims. Total inclusion of the guest within the cavity is apparent.

The optimal favorable interaction between Pr_2OD and β-CD in vacuum is shown in Figure 5 involves the carbonyl group interacting with hydroxyl group at the wide rim, one of the propyl group appears to be totally included within the cavity, while the other remains protruding outside the wide rim. The oxadiazole nucleus appears to be totally within the cavity of β-CD.

The optimal favorable interaction between Bu_2OD and β-CD in both environments, involves the oxadiazole oxygen is interacting with glucoside ether linkages, while

Table 2. $E_{binding}$ at the minimum energy and at the largest separation for H_2OD in water*

Energy, kcal/mol	H_2OD_{min}	H_2OD_{∞}
$E_{binding}$	−14.51	−0.20
Electrostatic part	−1.74	−0.14
Van der Waals part	−12.77	−0.061
E_{tot} for H_2OD/β-CD	127.46	141.71
Electrostatic part	−29.47	−27.83
Van der Waals part	21.97	34.70
Stretching + bending + torsion	134.96	136.05
E_{tot} for β-CD	122.34	122.19
Electrostatic part	−13.92	−13.88
Van der Waals part	35.32	35.11
Stretching + bending + torsion	100.94	100.96
E_{tot} for H_2OD	19.63	19.67
Electrostatic part	−14.02	−14.04
Van der Waals part	−0.48	−0.47
Stretching + bending + torsion	34.13	34.18

* The reference atom and β-CD structure are totally restricted.

Table 3. Binding energies of solute–ligand complexes (SL complexes) of R_2OD in vacuum and water*

Compound	Min/Å	Binding Energy kcal/mol
H_2OD	Vacuum -4	−20.57
	Water -2	−17.23
Me_2OD	Vacuum -1	−24.82
	Water -2	−21.24
Et_2OD	Vacuum -1	−27.61
	Water -2	−23.58
Pr_2OD	Vacuum -2	−31.44
	Water -2	−26.80
Bu_2OD	Vacuum -2	−33.80
	Water -1	−29.10

*All restrictions are removed from the system.

the two carbonyls groups interacting with both hydroxyls at narrow and wide rims. The oxadiazole groups appear totally included within the β-CD cavity. The alkyl groups appear to be outside the cyclodextrin rims.

A plot of $E_{binding}$ against the number of methylene groups (N) in the alkyl chain is linear in vacuum and in water as depicted in Figure 6. It is noteworthy that there is an almost constant increment (~4 kcal/mol; Figure 6; Table 3) for each extra methylene group in the alkyl chain for the studied series. This might be attributed to the expected increase in the favorable interactions as the length of the alkyl chain increases.

When calculations were performed in the presence of water as a solvent, a measure of the influence of the solvent on complexation was obtained using the following relation

$$E_{R_2OD/\beta\text{-CD}-water} = E_{R_2OD:\beta\text{-CD}+water} - (E_{R_2OD:\beta\text{-CD}} = E_{water})$$

where the terms on the right-hand side represent the potential energy of the whole system, $E_{R_2OD:\beta\text{-CD}+water}$, minus the sum of the energy of the water molecules, E_{water}, contained in solvent box without taking into account the presence of guest and β-CD, and the

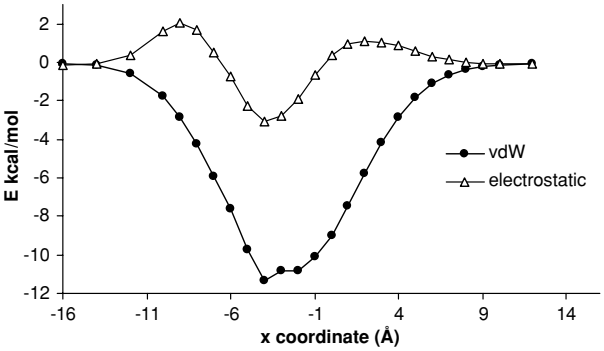

Figure 4. Van der Waals and electrostatic interactions for H_2OD/β-CD complex vs x coordinate (Å) in vacuum.

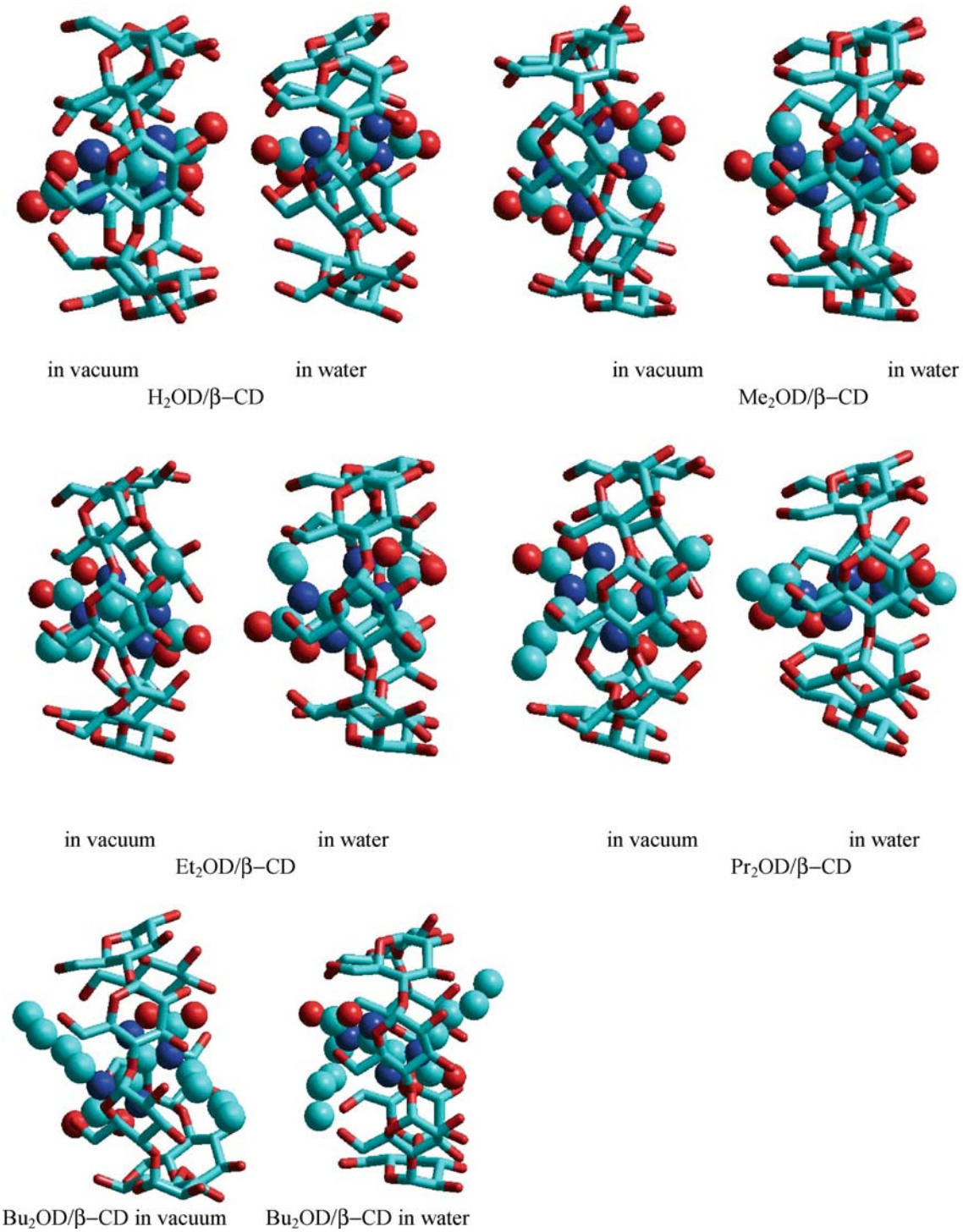

Figure 5. Side views of the most probable geometries of R_2OD/β-CD complexes in vacuum and in water. Hydrogen atoms are not drawn for sake of clarity.

potential energy of the system R_2OD:β-CD by removing the water molecules from the box, $E_{R_2OD:\beta\text{-CD}}$.

The energy of the interaction of the solvent with the complexes, denoted by , is depicted in Figure 7. Both guest to host approaches are accompanied by an increase of this energy that contributes significantly to destabilize the system. This fact was observed by other workers [18, 21, 25] in the study of other inclusion complexes. Therefore the hydration energy serves as a source of destabilization for the R_2OD complexes.

To verify our method, an *ab initio* MP2/6-311G** study was used to obtain geometry and binding energy of H_2OD/β-CD complex in vacuum. The MP2 energy was only calculated at the energy minimum (global minimum energy structure obtained by MM + optimization) in a single point computation. The calculation at the MP2 level used the frozen-core approximation (neglect of inner shell molecular orbitals in correlation calculations). The two-electron integral buffers were 3200 words (double precision) long and the two-electron

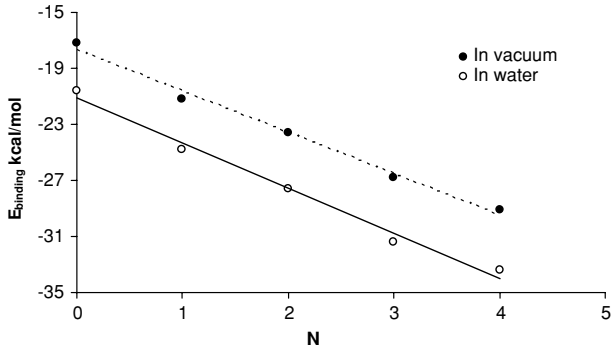

Figure 6. $E_{binding}$ vs the number of methylene groups (N) for R_2OD in vacuum and in water.

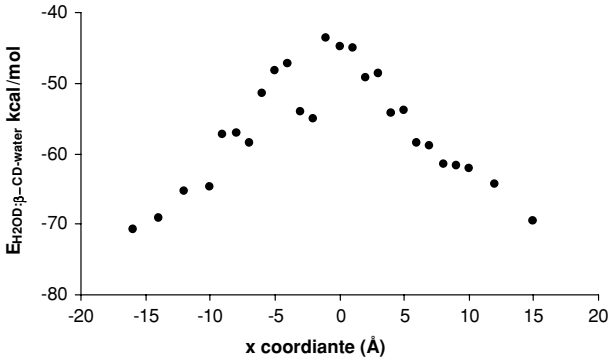

Figure 7. Interaction energy between water and H_2OD/β-CD complex.

integrals used a cut-off of 1×10^{-10}. The regular integral format was used. No extra orbitals were added to the bases set, and five d-orbitals were used. The binding energy for the minimum structure using MP2/6-311G** was found to be (−15.17 kcal/mol) which supports the calculated value obtained by our MM + calculation (−14.41 kcal/mol).

Conclusions

The more stable structures and the inclusion process for β-CD inclusion complexes were studied by means of molecular mechanics. The driving forces for complexation are dominant by non-bonded van der Waals interaction between the host and the guest, while the effect of electrostatic interactions is little. Longer and more flexible alkyl chain at 1,2,4-oxadiazole enhances complex stability. Therefore, the stability of the R_2OD/β-CD increases as the length of the alkyl chain increases indicating more favorable interactions. Each methylene group in bisoxadiazole contributes in stabilization of R_2OD/β-CD complexes to about 4 kcal/mol. The structure with the global minimum binding energy for R_2OD/β-CD complexes is characterized by the complete penetration of the oxadiazole bulk into the cavity of the CD.

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References

1. J. Cao, L. Huang, C. Zhao, S. Xu, X. Wang, and L. Wang: *Toxicol. Environ. Chem.* **76**, 73 (2000).
2. J. Cao, C. Zhao, L. Huang, Y. Ding, L. Wang, and S. Han: *Chemosphere* **40**, 1411 (2000).
3. S. Nigam and G. Durocher: *J. Phys. Chem.* **100**, 7135 (1996).
4. J. Velasco, P. Guardado, C. Carmona, M.A. Muñoz, and M. Balón: *J. Chem. Soc., Faraday Trans.* **94**, 1469 (1998).
5. N. Sanramé, R.H. de Rossi, and G.A. Argiiello: *J. Phys. Chem.* **100**, 8151 (1996).
6. T. Bojionova, Y. Coppel, N.L. Viguerie, A. Milius, I. Rico-Lattes, and A. Lattes: *Langmuir* **19**, 5233 (2003).
7. M. Ohashi, K. Kasatani, H. Shinohara, and H. Sato: *J. Am. Chem. Soc.* **112**, 5824 (1990).
8. N. Kawasaki, M. Arkai, T. Nakamura, and S. Tanada: *J. Coll. Interface Sci.* **238**, 215 (2001).
9. E. Junquera, D. Ruiz, and E. Aicart: *J. Coll. Interface Sci.* **216**, 154 (1999).
10. O. Bekers, E.V. Ujtendaal, J.H. Beijnen, A. Bult, and W.J. Underberg: *Drug Dev. Ind. Pharm.* **14**(11), 1503 (1991).
11. M. Ohashi, K. Kasatani, H. Shinohara, and H. Sato: *J. Am. Chem. Soc.* **112**, 5824 (1990).
12. V.B. Luzhkow and C.A. Venanzi: *J. Phys. Chem.* **99**, 2312 (1995).
13. M. Stodeman, U. Berg, and A. Svenssen: *J. Chem. Soc., Faraday Trans.* **94**, 1737 (1998).
14. M. Oana, A. Tintaru, D. Gavriliu, O. Maior, and M. Hillebrand: *J. Phy. Chem. B* **106**, 257 (2002).
15. B.S. Jursic, Z. Zdravkovski, and A.D. French: *J. Mol. Struct. (Theochem)* **366**, 113 (1996).
16. D. Salvatiorra, C. Jaime, A. Virgili, and F. Sanchez-Ferrando: *J. Org. Chem.* **61**, 9578 (1996).
17. G. Fronza, A. Mele, E. Redenti, and P. Ventura: *J. Org. Chem.* **61**, 909 (1996).
18. J. Madrid, J. Pozuelo, F. Mandicuti, and W.L. Mattice: *J. Coll. Interface Sci.* **193**, 11 (1997).
19. R.V. Belosludov, H. Mizuseki, K. Ichinoseki, and Y. Kawazoe: *Jpn. J. Appl. Phys.* **41**, 2739 (2002).
20. K.B. Lipkowitz: *Chem. Rev.* **98**, 1829 (1998).
21. M. Cervero and F. Mendicuti: *J. Phys. Chem. B* **104**, 1572 (2000).
22. P. Jiang, H-W. Sun, R-X. Shen, J. Shi, and C-M. Lai: *J. Mol. Struc. (Theochem)* **528**, 211 (2000).
23. K.A. Al-Sou′od, F.I. Khalili, and M.S. Mubarak: *J. Saudi Chem. Soc.* **4**(2), 143 (2000).
24. T-X. Lü, D-B. Zhang, and S-J. Dong: *J. Chem. Soc.* **285**(9),1439.
25. J.M. Madrid, F. Mendicuti, and W.L. Mattice: *J. Phys. Chem. B* **102**, 2037 (1998).
26. X. Sanchez-Ruiz, M. Ramos, and C. Jaime: *J. Mol. Struct. (Theochem)* **442**, 93 (1993).
27. F. Perez, C. Jaime, and X. Sanchez-Ruiz: *J. Org. Chem.* **60**, 3840.
28. K. Harata: *Bull. Chem. Soc. Jpn.* **55**, 2315 (1982).